

PROPHYLACTIC ADMINISTRATION OF RESPIRATORY SYNCYTIAL VIRUS IMMUNE GLOBULIN TO HIGH-RISK INFANTS AND YOUNG CHILDREN

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Abstract Background. Infants with cardiac disease or prematurity are at risk for severe illness caused by respiratory syncytial virus. Immune globulin with a high titer of antibodies against respiratory syncytial virus may offer infants and young children at risk protection from this serious, common respiratory illness.

Methods. We studied 249 infants and young children (mean age, eight months) who had bronchopulmonary dysplasia due to prematurity ($n = 102$), congenital heart disease ($n = 87$), or prematurity alone ($n = 60$). Respiratory syncytial virus immune globulin was given monthly to some of these children in either a high dose (750 mg per kilogram of body weight; $n = 81$) or a low dose (150 mg per kilogram; $n = 79$); 89 controls received no immune globulin. Group assignments were random. Assessments of respiratory illness and management were conducted without knowledge of the children's group assignments.

Results. There were 64 episodes of respiratory syncytial virus infection: 19 in the high-dose group, 16 in the low-dose group, and 29 in the control group. In the

high-dose group there were fewer lower respiratory tract infections (7, vs. 20 in the control group; $P = 0.01$), fewer hospitalizations (6, vs. 18 in the control group; $P = 0.02$), fewer hospital days (43, vs. 128 in the control group; $P = 0.02$), fewer days in the intensive care unit ($P = 0.05$), and less use of ribavirin ($P = 0.05$). In the low-dose group there was a significant reduction only in the number of days in the intensive care unit ($P = 0.03$). Adverse events during the 580 infusions were generally mild and included fluid overload (in five children), oxygen desaturation (eight), and fever (six). Six children died: three in the high-dose group, three in the low-dose group, and none in the control group ($P = 0.15$), but no death was attributed to the use of immune globulin or to illness caused by respiratory syncytial virus.

Conclusions. Administration of high doses of respiratory syncytial virus immune globulin is a safe and effective means of preventing lower respiratory tract infection in infants and young children at high risk for this disease. (N Engl J Med 1993;329:1524-30.)

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RESPIRATORY syncytial virus is an important respiratory pathogen of infancy and early childhood.^{1,4} The greatest morbidity and mortality occur among children at high risk for respiratory syncytial virus infection who are less than two years old⁵⁻⁷; these include preterm infants who are less than six months old⁸⁻¹⁰ and young children with underlying pulmonary or cardiac disease.¹¹⁻¹⁶ Currently, there are no safe and effective methods of actively immunizing infants against respiratory syncytial virus. However, studies in animals¹⁷⁻²² and epidemiologic observations in full-term infants^{5,6,23-26} indicate that the maintenance of serum titers of respiratory syncytial virus-

neutralizing antibody between 1:200 and 1:400 prevents respiratory syncytial virus infection in the lower respiratory tract.

Monthly infusions of a standard intravenous immune globulin are feasible and safe in high-risk infants. However, the peak titers of respiratory syncytial virus-neutralizing antibody achieved with commercial immune globulin at a dose of 750 mg per kilogram of body weight averaged only 1:87, well below the levels needed for protection.²⁷ An intravenous immune globulin is now available that contains high titers of respiratory syncytial virus-neutralizing antibody.²⁸ Our hypothesis was that respiratory syncytial virus infection of the lower respiratory tract could be attenuated or prevented in high-risk children by monthly infusions of respiratory syncytial virus immune globulin during the season when most respiratory syncytial virus infections occur (December through March or April).

METHODS

Patients

The study population was drawn from five clinical centers: University Hospital and the Children's Hospital, Denver; Strong Memorial Hospital, Rochester, New York; Children's National Medical Center, Washington, D.C.; the Floating Hospital, Boston; and Children's Hospital of Buffalo, Buffalo, New York. Children were enrolled if they were less than 48 months old at the beginning of the study (with children younger than 12 months preferred) and had congenital heart disease or cardiomyopathy, bronchopulmonary dysplasia, or premature delivery (≤ 35 weeks) and a chronologic age of less than 6 months. Reasons for exclusion were immunodeficiency, poorly controlled heart or renal failure, dependence on a ventilator, or an expected survival of less

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than six months. We followed the children during a single respiratory syncytial virus season, during which those assigned to the high-dose and low-dose groups received respiratory syncytial virus immune globulin, then through the next season. A "season" extended from December through March or April, depending on the presence of respiratory syncytial virus in the community. This study was approved by the investigational review board at each clinical site. Parents gave informed consent before their child's enrollment.

Study Design

The children were randomly assigned to one of three groups at each center: a high-dose group that received 750 mg of respiratory syncytial virus immune globulin per kilogram (15 ml per kilogram) each month; a low-dose group that received 150 mg of respiratory syncytial virus immune globulin per kilogram (3 ml per kilogram) each month; or a control group that received no respiratory syncytial virus immune globulin. Four separate lots of lyophilized human respiratory syncytial virus immune globulin with titers ranging from 1:2400 to 1:8073 were used over the three-year study period.²⁸

The sample size was determined on the basis of two primary end points: reduction in the incidence of lower respiratory tract infection caused by respiratory syncytial virus and reduction in the severity of respiratory syncytial virus disease. We calculated that a cohort of 250 children would be sufficient to guarantee a power of 80 percent with a type I error of 5 percent to detect a reduction in the incidence of respiratory syncytial virus infection of the lower respiratory tract from 25 percent among the controls to 10 percent among the treated children and a reduction in severity as measured by a composite respiratory score from moderate to mild in the treated groups.

The respiratory scoring system used in this study was based on changes in oxygen saturation and respiratory rate and on pulmonary findings of retractions (indrawing of chest wall), wheezing, and crackles.²⁹ For each of these variables, a score from 0 to 5 was determined by the degree of difference between the observed measurement and the child's base-line measurement. An overall respiratory score from 0 to 5 was calculated as the mode of the three component scores or the mean, if there was no mode (Table 1).

Study Visits and Infusions

Base-line epidemiologic and clinical data were obtained for each child at entry, and infusions were initiated in mid-November. Children in the two treated groups received three to five infusions at four-week intervals, depending on the length of the respiratory syncytial virus season at each center. The season was determined by observation of respiratory syncytial virus activity by the sentinel laboratories at each site. Low-dose infusions were given over a one-hour period, and high-dose infusions over a two-hour period, by constant-infusion pump. Vital signs were recorded every hour; the children were observed carefully for cardiac or pulmonary decompensation, respiratory scores were determined at the beginning and end of the infusion period, and adverse events and complications were recorded. A successful infusion was defined as receipt of at least 75 percent of the scheduled volume of the infusion. When a child missed a study visit, the family was called to reschedule the visit within two weeks.

Blinding and Surveillance

The nature of the study design required two separate teams at each clinical site. An unblinded team was responsible for the enrollment of patients and for all well-baby visits and examinations at the time of infusions. The blinded team was responsible for weekly

Table 1. Derivation of the Respiratory Score.*

OXYGEN SATURATION	RESPIRATORY RATE	RETRACTIONS, WHEEZING, CRACKLES
0 = Base-line value (no URTI)	0 = Base-line value (no URTI)	0 = No change (no URTI)
1 = Base-line value (URT)	1 = Base-line value (URT)	1 = Minimal
2 = Decrease <5%	2 = Increase 1-14/min	2 = Mild
3 = Decrease 5-10%	3 = Increase 15-30/min	3 = Moderate
4 = Decrease >10%	4 = Increase >30/min	4 = Severe
5 = Assisted ventilation	5 = Assisted ventilation	5 = Assisted ventilation
RESPIRATORY SCORE		
0 = Base-line value (well)		
1 = URTI		
2 = Mild LRTI		
3 = Moderate LRTI		
4 = Severe LRTI		
5 = Assisted ventilation		

*The respiratory score is the mode of the three component scores, or the mean if there is no mode. Values for oxygen saturation, respiratory rate, and pulmonary findings are compared with base-line values on usual oxygen flow. URTI denotes upper respiratory tract infection, and LRTI lower respiratory tract infection.

telephone surveillance for respiratory illness and for the evaluation of all respiratory illness. The parents were instructed not to divulge their child's treatment status to this second team. Separate case-report forms were used for each team. Ill children were evaluated only by a blinded member. A nasopharyngeal specimen obtained by nasal washing was submitted for rapid detection of respiratory syncytial virus antigen and respiratory-virus culture.³⁰ A respiratory syncytial virus infection was defined as existing when there was a positive test for respiratory syncytial virus antigen (by direct immunofluorescence or enzyme immunoassay, depending on the preference of the staff at each center^{30,31}) or isolation of respiratory syncytial virus in culture. Ill children who did not require hospitalization were assessed every two to three days by a blinded staff member until their base-line scores were achieved. The decision to hospitalize a child was also made by a blinded physician, and hospitalized children were evaluated daily. The decision to use ribavirin, to admit a child to the intensive care unit, to initiate mechanical ventilation, or to discharge a child from the hospital was made by an attending physician not involved with the study and unaware of the patient's treatment status.

During the subsequent respiratory syncytial virus season, the families of the children studied in the previous year were telephoned by blinded team personnel every other week. If respiratory syncytial virus illness developed, the children were evaluated as described above.

Statistical Analysis

Data were entered in duplicate into the Epi-Info data-entry program, cross-checked for accuracy of entry, and analyzed with Epi-Info version 5.01B, Statistical Analysis Systems version 6.07, and BMDP version 1990 software. All analyses were performed according to the intention-to-treat rule. The three treatment groups were compared with respect to sociodemographic variables and other potential risk factors by the two-tailed chi-square test. The incidence of disease and the frequency of hospitalization and admission to the intensive care unit were reduced to binary variables by counting only the first occurrence of each. Fisher's exact test was used when the outcome was binary and the expected number of occurrences in a group was less than five. Both the high-dose group and the low-dose group were compared with the control group with respect to efficacy and safety. Continuous measures, such as differences between groups in the mean number of days in the hospital and in the intensive care unit, were compared with the two-tailed t-test. This test was also used to compare the individual components of the respiratory score. The Wilcoxon rank-sum test was used to compare the worst respiratory scores among the treatment groups. For multivariate analyses, factors whose individual association with the primary end point, respiratory syncytial virus infection of the lower respiratory tract, achieved a P value of less than 0.05 were

included in a logistic-regression model used to assess the independent effect of treatment with respiratory syncytial virus immune globulin.

RESULTS

Characteristics of the Study Subjects

A total of 249 children were enrolled in the study. We found no significant differences among the treatment groups at the various study centers with respect to any demographic characteristics. Although a history of hospitalization for proved respiratory syncytial virus illness was more common in the high-dose group ($P = 0.05$) (Table 2), the base-line titers of respiratory syncytial virus A_2 -neutralizing antibody and the base-line respiratory scores were comparable in the three groups.

Compliance and Intravenous Access

In both the high- and the low-dose treatment groups, there was at least one problem with intravenous access in 60 percent of the children. However, at least 75 percent of the prescribed dose of respiratory syncytial virus immune globulin was infused at 85 percent of the visits. Compliance with the monthly visits was better in the treated groups; children who were receiving high-dose respiratory syncytial virus immune globulin missed 10 of 319 visits (3.1 percent), children receiving low-dose immune globulin missed 21 of 322 visits (6.5 percent), and control children missed 34 of their 376 monthly visits (9.0 percent) ($P = 0.006$ by the chi-square test).

Efficacy

Data on all 249 children were analyzed for efficacy. Only the first occurrence of a new illness or treatment event in a given patient was included in the analysis. The frequency of all lower respiratory tract infections was reduced by 48 percent, and the frequency of moderate and severe lower respiratory tract infections was reduced by 62 percent. These decreases were primarily due to the reduction in the rate of respiratory syncytial virus infection of the lower respiratory tract. Recipients of high-dose respiratory syncytial virus immune globulin had a 62 percent reduction in the incidence of respiratory syncytial virus infection of the lower respiratory tract ($P = 0.01$) and a 72 percent reduction in all moderate or severe respiratory syncytial virus infections of the lower respiratory tract ($P = 0.03$) (Table 3). The milder respiratory syncytial virus disease was reflected by lower respiratory scores in the high-dose group (mean \pm SD, 1.58 ± 0.21 vs. 2.34 ± 0.25 in the control group; $P = 0.01$). Recipients of the low dose of immune globulin did not have significantly lower scores than the controls (2.13 ± 1.8 , $P = 0.78$). Furthermore, children who received a low-dose infusion had a reduction of only 27 percent in the overall frequency of respiratory syncytial virus infections of the lower respiratory tract, as compared with the controls ($P = 0.35$), and a reduction of 53 percent in moderate or severe respiratory syncy-

tial virus infection of the lower respiratory tract ($P = 0.13$).

Children in the high-dose group were hospitalized 63 percent less often than control children (Table 4), and spent significantly fewer total days in the hospital for respiratory syncytial virus disease (a 63 percent reduction). Fewer admissions to the intensive care unit were observed in both the low-dose and the high-dose group than in the control group, and the total number of days in the intensive care unit was reduced by 97 to 100 percent over that for the controls (Ta-

Table 2. Demographic and Clinical Characteristics of 249 Infants and Young Children, According to Study Group.*

CHARACTERISTIC	HIGH DOSE (N = 81)	LOW DOSE (N = 79)	CONTROL (N = 89)
Mean age \pm SD (mo)	8.4 \pm 6.1	7.6 \pm 6.1	8.4 \pm 7.2
	number (percent)		
Male sex	46 (57)	39 (49)	56 (63)
Race or ethnic group			
White	49 (60)	56 (71)	52 (58)
Black	23 (28)	17 (22)	26 (29)
Hispanic	9 (11)	6 (8)	9 (10)
Asian	0	0	2 (2)
Insurance status			
Insured	39 (48)	50 (63)	45 (51)
Uninsured	42 (52)	29 (37)	44 (49)
Age at enrollment			
<12 mo	61 (75)	67 (85)	70 (79)
12-23 mo	17 (21)	9 (11)	17 (19)
\geq 24 mo	3 (4)	3 (4)	2 (2)
Diagnostic group			
Bronchopulmonary dysplasia	37 (46)	28 (35)	37 (42)
Congenital heart disease	23 (28)	33 (42)	31 (35)
Prematurity (no bronchopulmonary dysplasia)	21 (26)	18 (23)	21 (24)
No. of persons in the home			
<3	29 (36)	25 (32)	29 (33)
3-5	40 (49)	47 (59)	48 (54)
\geq 6	12 (15)	7 (9)	12 (13)
Atopy in the family	32 (40)	27 (34)	26 (29)
Cigarette smoking by parents	40 (49)	39 (49)	41 (46)
Previous respiratory syncytial virus infection	10 (12)	4 (5) [†]	3 (3) [†]
	titer		
Base-line respiratory syncytial virus [‡]	1:23	1:17	1:20

*Because of rounding, percentages may not total 100.

[†] $P = 0.05$ (by the chi-square test) for the comparison with the high-dose group.

[‡]Geometric mean respiratory syncytial virus-neutralizing antibody titer.

ble 4). Two children in the control group and none in either treatment group required assisted ventilation. A significant decrease in the number of days of ribavirin use was also observed in the high-dose group (9 per 100 children) as compared with the control group (33 per 100 children, $P = 0.05$).

Although there was a reduction in the incidence of respiratory syncytial virus infection of the lower respiratory tract and hospitalization for respiratory syncytial virus illness in all three groups, the greatest improvement was among preterm infants and infants

with bronchopulmonary dysplasia. The controls at the Denver center differed from those at the other four centers in that respiratory syncytial virus infection of the lower respiratory tract occurred more frequently among these children and was more severe, as defined by the need for hospitalization (33 percent vs. 14 percent). These differences probably reflect the effect of altitude on the severity of respiratory tract disease.^{8,11,12}

We constructed a multivariate model to examine

Table 3. Incidence of Acute Respiratory Disease and Respiratory Syncytial Virus (RSV) Infection, According to Study Group.

DISEASE*	HIGH DOSE (N = 81)	LOW DOSE (N = 79)	CONTROL (N = 89)	P VALUE	
				HIGH DOSE VS. CONTROL	LOW DOSE VS. CONTROL
Acute respiratory disease	84	93	101	0.79	0.96
RSV	19	16	29	0.19	0.08
Non-RSV	65	77	72	0.99	0.49
LRTI†	21	35	44	0.007	0.74
RSV	7	13	20	0.01	0.35
Non-RSV	14	22	24	0.20	0.79
Moderate to severe LRTI‡	5	9	17	0.02	0.21
RSV	3	5	12	0.03	0.13
Non-RSV	2	4	5	0.45	0.99

*Only the first episode of each illness in each child is included. LRTI denotes lower respiratory tract infection.

†Defined as an acute lower respiratory tract illness with a respiratory score of 2 or more.

‡Defined as an acute lower respiratory tract illness with a respiratory score of 3 or more.

the protective effect of treatment with respiratory syncytial virus immune globulin in combination with recognized risk factors for respiratory syncytial virus illness on the presence or absence of respiratory syncytial virus infection of the lower respiratory tract. The study center, male sex, a higher number of people in the household, and a history of respiratory syncytial virus illness were all related to a higher incidence of respiratory syncytial virus infection. After adjustment for these variables, treatment with high-dose respiratory syncytial virus immune globulin reduced the incidence of respiratory syncytial virus infection of the lower respiratory tract by 75 percent ($P = 0.009$), whereas the reduction in incidence associated with low-dose immune globulin was not significant (44 percent, $P = 0.24$).

The Timing of Infusions

We examined the timing of respiratory syncytial virus illness in relation to the infusions of respiratory syncytial virus immune globulin and in relation to the monthly visits in the case of the control children. All episodes of respiratory syncytial virus infection of the lower respiratory tract occurred within 40 days of a completed infusion among the children receiving high-dose infusions at a mean interval of 24.8 ± 18.9 days. This was comparable to the interval between treatment and the development of respiratory syncy-

Table 4. Hospitalization for Respiratory Syncytial Virus Infection of the Lower Respiratory Tract, According to Study Group.*

VARIABLE	HIGH DOSE (N = 81)	LOW DOSE (N = 79)	CONTROL (N = 89)	P VALUE	
				HIGH DOSE VS. CONTROL	LOW DOSE VS. CONTROL
Hospitalizations	6	10	18	0.02	0.19
Days in hospital†	43	63	128	0.02	0.12
Admissions to ICU	1	0	6	0.12	0.03
Days in ICU†	1	0	34	0.05	0.03

*Only the first hospitalization for each child is included. ICU denotes intensive care unit.

†Numbers shown are the total number of hospital days for each child.

tial virus in children receiving low-dose infusions (20.3 ± 12.7 days) and between illness and the monthly visits in control children (22.3 ± 13.1 days).

Tolerance and Safety

Nineteen acute adverse reactions occurred among 580 infusions (3 percent). Five infants were thought to have mild fluid overload; two of them had findings of fluid overload before the infusion began. All five responded to the slowing of the rate of infusion or to the administration of diuretics; most received subsequent infusions without problems. The remaining adverse reactions consisted of mild decreases in oxygen saturation (in eight children) and fever (in six). The only serious event occurred in a 17-month-old infant with severe bronchopulmonary dysplasia; after a second dose of 750 mg of respiratory syncytial virus immune globulin per kilogram he had fever (temperature, 40.6°C), crackles, and increasing respiratory distress, which necessitated mechanical ventilation within 24 hours. This child died of progressive respiratory failure three months later.

Respiratory Disease in Subsequent Seasons

Eighty-five percent of the children (210 of 249) were followed during a second respiratory syncytial virus season. Of these, 18 children in the high-dose group, 11 in the low-dose group, and 14 controls had respiratory syncytial virus illness ($P = 0.89$ by the chi-square test). Five children in the high-dose group, five in the low-dose group, and seven in the control group required hospitalization for respiratory syncytial virus disease. The observed rate of rehospitalization was consistent with that seen in children with chronic lung or heart disease.^{32,33}

Deaths

Over the three-year study period, six deaths occurred after the initial infusion and within the four months after the last infusion. There were three deaths in the high-dose group, three in the low-dose group, and none in the control group ($P = 0.15$ by Fisher's exact test). Extensive analysis of hospital and autopsy reports revealed no basis for attributing the deaths to the infusion of respiratory syncytial virus immune globulin (Table 5). No death occurred as a result of

respiratory syncytial virus infection. Because 5 of the children had heart disease, the entire cohort of 87 patients with cardiac disorders was analyzed separately by a pediatric cardiologist blinded to their group assignment. No differences in the type of cardiac abnormality, changes in cardiac status, or frequency of cardiac surgery were observed. Three deaths were directly associated with complications of cardiac surgery and occurred 2 to 13 weeks after the final infusion of respiratory syncytial virus immune globulin. The remaining three deaths were due to medical causes and occurred two weeks, one month, and three months after an infusion (Table 5).

DISCUSSION

Monthly infusions of high-dose immune globulin containing high titers of respiratory syncytial virus-neutralizing antibody significantly decreased both the incidence and the severity of respiratory syncytial virus infection of the lower respiratory tract in children at high risk for this disease. High-dose respiratory syncytial virus immune globulin had a significant effect on the frequency of respiratory syncytial virus-associated hospitalization (a 63 percent reduction), the total number of days of hospitalization (a 63 percent reduction), and the number of days in the intensive care unit (a 97 percent reduction). The children who received low-dose respiratory syncytial virus immune globulin were comparable to those who received the high dose only in the reduction in the total number of days in the intensive care unit for illness associated with respiratory syncytial virus.

The trough serum titers of respiratory syncytial virus-neutralizing antibody among the children in the high-dose group generally exceeded 1:200.³⁴ Thus, our study findings were consistent with those of studies in animals in which respiratory syncytial virus-neutralizing antibody titers between 1:200 and 1:400 conferred protection against pulmonary infection.^{20,21} Prophylaxis with respiratory syncytial virus immune globulin was effective in children in this study with all three types of diagnosis, but it appeared particularly efficacious in preterm infants with or without bronchopulmonary dysplasia. Preterm infants, particularly those delivered at less than 32 weeks' gestation,

have very little maternal respiratory syncytial virus-neutralizing antibody³⁵ and may have particularly severe respiratory syncytial virus illness.^{36,37} Such infants would be expected to benefit from passive immunization with immune globulin with respiratory syncytial virus-neutralizing antibody.

There were few adverse events during the immune globulin infusions (3 percent), and those that occurred were similar to those observed in other studies in which intravenous immune globulin was used.³⁸⁻⁴⁰ The most difficult problem was obtaining intravenous access; despite this difficulty, however, most treated children received at least 75 percent of their scheduled infusions, and compliance with the examination schedule was significantly better in the treated groups than in the control group, suggesting that families felt that the potential prevention of severe respiratory illness was worth the inconvenience of added visits and infusions. Six children died between the initial infusion and four months after the last infusion. No child died of respiratory syncytial virus-related illness, and no relation between the infusion of respiratory syncytial virus immune globulin and death was found. Five children who died had cardiac disease; three of these deaths were directly attributable to complications of cardiac surgery. There was no evidence of an increased frequency or severity of subsequent respiratory syncytial virus illness among the children treated with the respiratory syncytial virus immune globulin. We are confident on the basis of these results that respiratory syncytial virus immune globulin is safe for preterm infants with or without bronchopulmonary dysplasia. Although there was no evidence that respiratory syncytial virus immune globulin worsened cardiac disease, its safety in children with cardiac disorders merits further examination.

The results of this trial justify the evaluation of respiratory syncytial virus immune globulin as prophylaxis against severe respiratory syncytial virus illness in other high-risk groups of children and adults. Our findings should provide an impetus for the development of additional methods of passive immunoprophylaxis, such as the intramuscular administration of monoclonal antibodies.^{41,42} The finding that prophy-

Table 5. Deaths during the Study.*

TREATMENT GROUP	AGE (MO)	DIAGNOSIS	DATE OF LAST INFUSION (No.)	DATE OF SURGERY	DATE OF DEATH	CAUSE OF DEATH
High dose	17	Bronchopulmonary dysplasia	1/24/91 (third)	—	4/23/91	Progressive respiratory failure
High dose	8	Tetralogy of Fallot with pulmonary atresia	2/8/91 (third)	2/26/91	2/27/91	Surgical (arrhythmia)
High dose	13	Tetralogy of Fallot	1/28/91 (third)	—	2/5/91	Pacemaker wire abscess; sudden death
Low dose	10	Pulmonary stenosis	2/27/91 (third)	4/16/91	7/13/91	Surgical (anoxic injury due to cardiac arrest)
Low dose	3	Atrioventricular canal	2/25/91 (second)	—	3/31/91	Congenital heart disease; pulmonary vascular disease
Low dose	8	Tetralogy of Fallot with pulmonary atresia	2/6/92 (third)	2/18/92	2/18/92	Surgical (hypotension, pulmonary hyperinflation)

*Three six deaths occurred after the first study infusion and within four months after the last infusion.

lactic monthly infusions of high-dose respiratory syncytial virus immune globulin reduced both the incidence and the severity of respiratory syncytial virus illness is clinically important, particularly because strategies of active immunization against respiratory syncytial virus in very young seronegative children are proceeding slowly,^{43,44} and no vaccine for universal use will be available for some time. Passive immunization with high-dose respiratory syncytial virus immune globulin is therefore currently the only safe and effective means of protecting high-risk infants and children against this serious illness.

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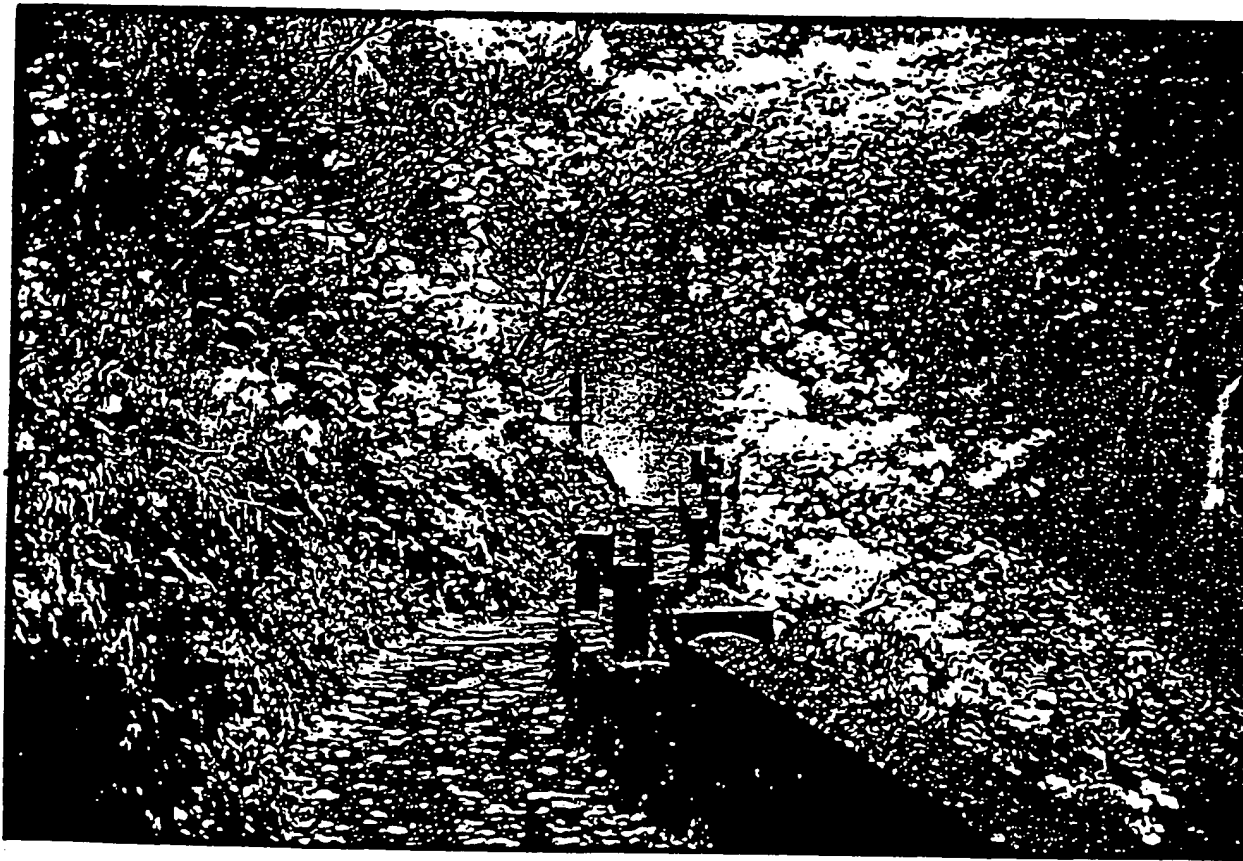
APPENDIX

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